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Predicting outcomes in colorectal endoscopic submucosal dissection: a United States experience

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Abstract

Objective Endoscopic submucosal dissection (ESD) allows for en bloc resection of superficial gastrointestinal neoplasms; however, US experience has been limited. We aimed to evaluate our clinical outcomes in colorectal ESD.

Design This prospective study included consecutive patients undergoing colorectal ESD at a major US center. Demographics, lesion and technical characteristics, outcomes, adverse events, and pathological diagnoses were recorded. Factors affecting resection outcomes and procedure time were evaluated.

Results 77 patients who underwent colorectal ESD were analyzed. Mean colorectal lesion diameter was 49.4 mm. Mean procedure time was 104.7 min, and 97.4% of patients were discharged home on the same day. En bloc, complete, and curative resection was achieved in 97.4%, 97.4%, and 93.5% of colorectal ESD cases. Microperforation and delayed bleeding rates were 1.3% and 3.9%. On univariable analysis, the presence of tattoo adversely affected en bloc resection ($p=0.002$), complete resection ($p=0.002$), and curative resection ($p=0.008$). Prior EMR attempts adversely affected en bloc resection ($p=0.028$), complete resection ($p=0.028$), and procedure time ($p=0.008$). On multivariable analysis, the presence of tattoo predicted failure to achieve curative resection (OR 0.13; 95% CI 0.02–0.98; $p=0.048$). Lesion size > 50 mm (OR 3.89; 95% CI 1.13–13.41; $p=0.031$), presence of tattoo (OR 9.38; 95% CI 1.05–83.83; $p=0.045$), and prior EMR attempts (OR 7.13; 95% CI 1.76–28.90; $p=0.006$) predicted procedure time ≥ 90 min. A scoring system was created to predict prolonged ESD procedure time and was externally validated, with AUC 0.78 (95% CI 0.73–0.83).

Conclusion This study demonstrates the effects of multiple risk factors on resection outcomes and procedure time in colorectal ESD. Tattoo placement and attempted EMR should be avoided for lesions being considered for ESD.

Keywords Endoscopic submucosal dissection · Endoscopic resection · Colorectal polyp · Colorectal neoplasia · Therapeutic endoscopy

Abbreviations

ANOVA	Analysis of variance
AUROC	Area under the receiver operating characteristics curve
CI	Confidence interval
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
EUS	Endoscopic ultrasound
LST	Laterally spreading tumor
LST-G	Laterally spreading tumor, granular type
LST-G (mixed)	Laterally spreading tumor, granular type, nodular mixed type
LST-G (uni)	Laterally spreading tumor, granular type, homogeneous type
LST-NG	Laterally spreading tumor, non-granular type
LST-NG (FE)	Laterally spreading tumor, non-granular type, flat-elevated type
LST-NG (PD)	Laterally spreading tumor, non-granular type, pseudo-depressed type
NBI	Narrow band imaging
SD	Standard deviation

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Endoscopic submucosal dissection (ESD) allows for the complete endoscopic resection of superficial gastrointestinal lesions, and has become the standard of care for resection of early gastrointestinal tumors in multiple Asian countries [1]. ESD usually achieves en bloc resection, which is often not achievable with endoscopic mucosal resection (EMR) especially when performed for larger lesions [2–4]. ESD also allows for greater rates of complete resection, reduced risk of tumor recurrence, and better ability to achieve an accurate histopathological diagnosis for oncologic staging [5–8].

Despite increasing literature detailing experiences in Asia and Europe, ESD has not been widely adopted in the US. This is thought to be due to multiple factors including technical difficulty and learning curve, increased procedure time, increased risk of adverse events, lack of adequate reimbursement structure, expensive hospitalization, and differences in epidemiology between Asian and Western countries with regard to gastric and colorectal neoplasia [9].

This study was conducted to assess the clinical outcomes of colorectal ESD in the US setting, and to determine clinical factors that are associated with outcomes in colorectal ESD. Our secondary goal was to develop a prognostication tool to predict prolonged procedural time for colorectal ESD.

Patients and methods

Patients

Between January 2015 and September 2017, consecutive adult patients who underwent ESD for treatment of gastrointestinal lesions were prospectively enrolled in a registry which was retrospectively analyzed for the purposes of this study. Patients were treated at the Brigham and Women's Hospital, a major academic referral center affiliated with Harvard Medical School in Boston, Massachusetts. Institutional Review Board approval was obtained for this study.

In accordance with institutional policy, exclusion criteria for ESD included small lesions that could be reliably resected in an en bloc fashion with EMR, lesions with endoscopic characteristics of deep submucosal invasion [10, 11], and lesions with lymph node or metastatic involvement as identified on endoscopic ultrasonography (EUS) or cross-sectional imaging.

ESD procedures

Following written informed consent, patients were sedated under conscious sedation or monitored anesthesia care. ESD was performed according to previously described techniques [8, 12, 13] by a single ESD expert (H.A.) with vast experience in both upper and lower ESD. All procedures were performed using carbon dioxide gas insufflation.

Lesions were identified and carefully examined using high-definition white light endoscopy and narrow band imaging (NBI) (GIF-HQ190 or PCF-H190L; Olympus America, Center Valley, PA, USA) with transparent distal attachment cap (Olympus America). Endoscopic tumor morphology was classified using the Paris endoscopic classification [14, 15]. Laterally spreading tumors (LST) were categorized as either granular type (LST-G), or non-granular type (LST-NG) [16, 17]. EUS using a 20 MHz miniprobe was performed for lesions with possible deep submucosal invasion.

A needle type (Dual Knife; Olympus America) and/or insulated tip ESD knife (IT-2 Knife or ITknife nano; Olympus America) was used for mucosal incision and submucosal dissection after lifting with highly viscous solution (hydroxypropyl methylcellulose or hydroxyethyl starch) per endoscopist's discretion. Hemostatic forceps (Coagrasper, Olympus America) were used for hemostasis and to eliminate visible vessels during or following resection.

During ESD, the degree of fibrosis was categorized from F0 to F2 using a previously defined scoring system [18]. Tattoo was considered positive when black deposit from ink injection was encountered during submucosal dissection. The presence of scar tissue from prior EMR attempts was noted.

Prophylactic mucosal defect closure was performed only for deep muscle injury or microperforation. Procedures were performed in an outpatient setting, and patients were hospitalized following the procedure only when clinically indicated. Delayed bleeding was defined as clinically significant bleeding that caused a drop of hemoglobin by >2 g/dL, or that required transfusion or endoscopic intervention. Perforation was diagnosed either endoscopically or by the presence of extraluminal air seen on radiographic imaging. Mortality was defined as any death within 30 days following ESD.

Histopathological evaluation of treatment outcomes

All excised specimens were fixed with pins on a board and submitted for evaluation by a gastrointestinal pathologist. Specimens were fixed in 10% buffered formalin, embedded in paraffin, and sectioned into pieces at 2 mm intervals. All slides were prepared for histological analysis including lesion size, invasion depth, presence of fibrosis, presence of carcinoma, and lateral and deep margins.

In cases of submucosal invasive carcinoma, further analysis was performed to evaluate treatment outcomes in accordance with Japanese ESD guidelines [4]. Elastica van Gieson staining and immunostaining with anti-lymphatic vessel endothelial antibody (D2-40) were used to evaluate for vascular and lymphatic invasion. A final pathological

diagnosis was rendered in accordance with the Vienna classification [19].

En bloc resection was defined as successful endoscopic removal of the lesion in a single piece. The resection was considered "complete" when the lesion was removed en bloc with pathologically negative margins (R0 resection). The resection was considered "incomplete" if either lateral or deep margins were positive for the lesion (R1 resection), or if margins could not be evaluated due to piecemeal resection or cautery artifact (Rx resection) [12]. The resection was considered "curative" only if the lesion underwent a complete resection with negative margins and did not have risk factors for lymph node metastasis such as deep submucosal invasion (cutoff depth of 1000 μm [20]), lymphovascular invasion, poor differentiation, or tumor budding.

Follow-up

All patients were scheduled for follow-up endoscopic examination at 6 months following ESD if complete resection was obtained, or 3 months if resection was piecemeal or resection margin was positive. At follow-up endoscopy, biopsy specimens were obtained from the treatment-related scar or any other adjacent suspicious abnormalities to evaluate for the presence of local recurrence or residual tumor.

In accordance with institutional policy, all patients with submucosal invasive carcinoma were referred for surgical resection with lymph node dissection regardless of invasion depth. If patients refused surgery, they were referred to a medical oncologist and underwent a strict surveillance protocol that included serial endoscopy, tumor markers, and cross-sectional imaging at regular intervals at the discretion of the oncologist.

Data analysis

Demographics were recorded including patient age and sex. Lesion characteristics were recorded including size, location, Paris and LST classification, presence of tattoo, prior EMR attempts, and endoscopic fibrosis score. Procedural characteristics were recorded including injection solution, electrosurgical knife, traction method, and closure method. Pathological outcomes were recorded including size and depth of lesion, lymphovascular involvement, tumor differentiation, tumor budding, and final pathological diagnosis. Clinical outcomes were recorded including en bloc, complete, and curative resection rates, procedure time, hospitalization rates and lengths of hospital stay, length of follow-up, recurrence rates, and adverse events such as bleeding, stricture, and perforation. If patients underwent surgery, the final pathological diagnosis from the surgical specimen was recorded.

Non-colorectal lesions were excluded in order to analyze resection outcomes and procedure time of colorectal ESD. Non-neoplastic lesions were also excluded from analysis of clinical outcomes given that these lesions are typically not indications for ESD, and outcomes such as resection margins, curative resection rates, and tumor recurrence cannot be evaluated for these lesions.

Statistics

Descriptive statistics were used to characterize the demographics of the study population. Categorical data were summarized using counts and percentages, and continuous data were summarized using means and standard deviation. Univariable analysis of factors affecting resection outcomes and procedure time was performed using Fisher's exact test when comparing categorical variables, and Student's *t* test or one-way analysis of variance (ANOVA) test when comparing continuous variables.

Factors affecting resection outcomes and procedure time were analyzed using a multivariable linear regression analysis. These factors were determined a priori and included lesion size, prior EMR attempts, and presence of tattoo. Endoscopic fibrosis scores were not included in the model given collinearity with prior EMR attempts and presence of tattoo.

Colorectal ESD procedural time scoring system development and validation

ESD procedural time was dichotomized into two groups: ≥ 90 min versus < 90 min. This cutoff was determined based on the median procedure time of our cohort. The prediction model for the dichotomized ESD procedural time was developed using a multivariable stepwise regression. A significance level of 0.05 was used for model entry and retention. The scoring system was developed using proportional weighing of the significant predictors based on the beta-coefficient of each variable. The scoring system for colorectal ESD procedure time was then externally validated using a Japanese colorectal ESD cohort from Jikei University School of Medicine. Area under the receiver operating characteristics curve (AUC) was reported.

P values of < 0.05 were considered statistically significant. Statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC).

Results

Demographics and technical characteristics

Demographics and ESD technical characteristics are shown in Table 1. A total of 100 consecutive patients underwent

ESD, of which 83 (83.0%) underwent colorectal ESD. The mean age was 64.0 (± 13.2) years, and 39.8% were male. There were 44 lesions in the right colon, 11 lesions in the left colon, and 28 lesions in the rectum. Most colorectal lesions (74/83, 89.2%) were laterally spreading tumors. The mean lesion diameter was 47.5 (± 27.7) mm, with 2.4% (2/83) of patients having lesions < 20 mm in diameter, 71.1% (59/83) of patients having lesions between 20 and 50 mm in diameter, 20.5% (17/83) of patients having lesions between 51 and 100 mm in diameter, and 6.0% (5/83) of patients having lesions > 100 mm in diameter. Lesions < 20 mm in diameter were non-lifting colonic EMR scars with prior positive margins.

Final pathology showed adenoma in 58 (69.9%) patients, high-grade dysplasia in 9 (10.8%) patients, intramucosal carcinoma in 5 (6.0%) patients, submucosal carcinoma in 5 (6.0%) patients, subepithelial lesions in 1 (1.2%) patients, and a benign mucosal lesion in 5 (6.0%) patients. The subepithelial lesion was a rectal lipoma, and benign mucosal lesions consisted of three rectal inflammatory lesions and two colonic EMR scars with prior positive margins that had no neoplasia on ESD.

After excluding the six non-neoplastic lesions, a total of 77 consecutive colorectal ESD cases were further analyzed for clinical outcomes.

Clinical factors and outcomes of colorectal ESD

Clinical factors and procedural outcomes of colorectal ESD are shown in Table 2. A previous tattoo affecting the dissection process was encountered in 16.9% (13/77) of cases, and prior EMR attempts were noted in 29.9% (23/77). Mild fibrosis was seen in 31.2% (24/77) and severe fibrosis in 23.4% (18/77) of cases.

The mean procedure time was 104.7 (± 50.4) min, of which 16.9% of cases were completed in ≤ 60 min, 64.9% were completed in 61–120 min, and 18.2% required > 120 min. The median procedure time was 90.0 min. En bloc resection was achieved in 97.4% (75/77), complete resection in 97.4% (75/77), and curative resection in 93.5% (72/77) of cases.

Adverse events and hospitalizations

There were a total of 4 (5.2%) adverse events, including 1 (1.3%) microperforation and 3 (3.9%) cases of delayed bleeding. Seventy-five (97.4%) patients were discharged home on the same day, while 2 (2.6%) patients required hospitalization for overnight observation due to delayed recovery from sedation ($n = 1$) and microperforation ($n = 1$).

There was no incidence of major perforation, peritonitis, or mortality. There was no recorded incidence of

Table 1 Demographics and technical characteristics

	Incidence (*n*, %)
Demographics	
Total patients	83
Mean age (± SD)	64.0 ± 13.2
Gender	
Male	33 (39.8)
Female	50 (60.2)
Location	
Right colon (cecum, ascending, transverse)	44 (53.0)
Left colon (descending, sigmoid)	11 (13.3)
Rectum	28 (33.7)
Morphology	
Paris Is	5 (6.0)
Paris Isp	1 (1.2)
LST-G (uni)	12 (14.5)
LST-G (mixed)	33 (39.8)
LST-NG (PD)	20 (24.1)
LST-NG (FE)	9 (10.8)
EMR scar	2 (2.4)
Subepithelial lesions	1 (1.2)
Injection solution	
Saline	2 (2.4)
Hydroxypropyl methylcellulose	10 (12.1)
Hydroxyethyl starch	71 (85.5)
Traction method	
None	66 (79.5)
Suture loop	1 (1.2)
Rubber band	14 (16.9)
Pocket creation	2 (2.4)
Lesion size	
Mean size (± SD, mm)	47.5 ± 27.7 mm
Size < 20 mm	2 (2.4)
Size 20–50 mm	59 (71.1)
Size 51–100 mm	17 (20.5)
Size > 100 mm	5 (6.0)
Pathology	
Adenoma	58 (69.9)
High-grade dysplasia	9 (10.8)
Intramucosal carcinoma	5 (6.0)
Submucosal carcinoma	5 (6.0)
Subepithelial lesions	1 (1.2)
Benign mucosal lesions	5 (6.0)

EMR endoscopic mucosal resection, *LST-G* (uni) laterally spreading tumor granular homogeneous type, *LST-G* (mixed) laterally spreading tumor granular nodular mixed type, *LST-NG (PD)* laterally spreading tumor non-granular pseudo-depressed type, *LST-NG (FE)* laterally spreading tumor non-granular flat-elevated type, *SD* standard deviation

Table 2 Clinical factors and outcomes of colorectal ESD

	Incidence (*n*, %)
Clinical factors	
Presence of existing tattoo	13 (16.9)
Prior EMR attempt	23 (29.9)
Size > 50 mm	22 (28.6)
Fibrosis	
F0 (no fibrosis)	24 (31.2)
F1 (mild fibrosis)	35 (45.5)
F2 (severe fibrosis)	18 (23.4)
Outcomes	
En bloc resection	75 (97.4)
Complete resection	75 (97.4)
Curative resection	72 (93.5)
Mean procedure time (± SD, min)	104.7 ± 50.4 min
Follow-up	
Mean follow-up time (± SD, months)	17.3 ± 8.7 months
Recurrence	0 (0.0)
Underwent surgery	3 (3.9)
Hospitalization	
Hospital admission	2 (2.6)
Adverse events	
Microperforation	1 (1.3)
Bleeding	3 (3.9)

n = 77 after excluding six non-neoplastic lesions

EMR endoscopic mucosal resection, *SD* standard deviation

changes in bowel habits, bowel obstruction, or colorectal stricture formation on short-term follow-up.

Non-curative resections and invasive carcinomas

The characteristics of non-curative resections and submucosal invasive carcinomas are shown in Table 3. Curative resection was not achieved in 5 (6.5%) patients. This included three patients with deep submucosal invasive carcinoma (invasion depth > 1000 μm) with negative margins, and two patients with piecemeal resection (Rx).

All five patients with submucosal invasive carcinoma, including two who had a curative resection, were referred for surgical consultation per institutional protocol. Of those, three patients underwent surgical resection, of which all had no evidence of residual carcinoma and negative lymph nodes on surgical pathology.

The other patients who refused surgery, as well as all remaining patients who had complete and curative tumor resection showed no clinical evidence of recurrence on follow-up. Mean follow-up was 17.3 (± 8.7) months.

Table 3 Non-curative resections and invasive carcinomas

Patient	Location	Morphology	Size (mm)	Tattoo	Prior EMR attempt	Fibrosis score	Complete resection	Curative resection	Pathology	Invasion depth (μm)	Follow-up
1	Rectum	LST-NG (PD)	30	No	No	F1	Yes	Yes	Submucosal carcinoma	220	No surgery, no evidence of recurrence
2	Cecum	LST-NG (PD)	51	No	Yes	F2	Yes	Yes	Submucosal carcinoma	890	Right hemicolectomy: no residual cancer, negative lymph nodes
3	Rectum	Paris Is	30	No	No	F1	Yes	No	Submucosal carcinoma	2250	Low anterior resection: no residual cancer, negative lymph nodes
4	Sigmoid	LST-NG (PD)	20	Yes	Yes	F2	Yes	No	Submucosal carcinoma	1830	Sigmoidectomy: no residual cancer, negative lymph nodes
5	Ascending	LST-NG (PD)	50	No	No	F1	Yes	No	Submucosal carcinoma	1650	No surgery, no evidence of recurrence
6	Descending	LST-NG (FE)	30	Yes	Yes	F2	No (piecemeal)	No	Tubular adenoma	N/A	No surgery, no evidence of recurrence
7	Rectum	LST-G (mixed)	72	Yes	Yes	F2	No (piecemeal)	No	Intramucosal carcinoma	N/A	No surgery, no evidence of recurrence

LST-G (mixed) laterally spreading tumor granular nodular mixed type, *LST-NG (PD)* laterally spreading tumor non-granular pseudo-depressed type, *LST-NG (FE)* laterally spreading tumor non-granular flat-elevated type

Factors associated with curative resection and procedure time

Factors associated with curative resection and procedure time are shown in Table 4 and Fig. 1. Both the en bloc resection rate and the complete resection rate were affected by the presence of tattoo (84.6% vs. 100%, $p=0.002$), prior EMR attempts (91.3% vs. 100%, $p=0.028$), and by severe fibrosis (88.9% vs. 100% for mild or no fibrosis, $p=0.035$). The en bloc resection rate and complete resection rate were not affected by size > 50 cm (95.5% vs. 98.2%, $p=0.497$). The curative resection rate was affected by the presence of tattoo (76.9% vs. 96.9%, $p=0.008$), but not by size > 50 mm (95.5% vs. 92.7%, $p=0.661$) or by prior EMR attempts

Table 4 Univariable analysis of impact of clinical factors on colorectal ESD outcomes

	En bloc resection (*n*, %)	*p* value	Complete resection (*n*, %)	*p* value	Curative resection (*n*, %)	*p* value	Procedure time (min)	*p* value
Risk factor: size								
Size ≤ 50 mm	54 (98.2)	0.497	54 (98.2)	0.497	51 (92.7)	0.661	90.8	**< 0.001**
Size > 50 mm	21 (95.5)		21 (95.5)		21 (95.5)		139.4	
Risk factor: tattoo								
Tattoo present	11 (84.6)	**0.002**	11 (84.6)	**0.002**	10 (76.9)	**0.008**	120.8	0.209
Tattoo absent	64 (100.0)		64 (100.0)		62 (96.9)		101.4	
Risk factor: prior EMR								
Prior EMR	21 (91.3)	**0.028**	21 (91.3)	**0.028**	20 (87.0)	0.128	127.8	**0.008**
No prior EMR	54 (100.0)		54 (100.0)		52 (96.3)		94.8	
Risk factor: fibrosis								
F0 (no fibrosis)	24 (100.0)	**0.035**	24 (100.0)	**0.035**	24 (100.0)	0.092	88.7	0.084
F1 (mild fibrosis)	35 (100.0)		35 (100.0)		33 (94.3)		106.0	
F2 (severe fibrosis)	16 (88.9)		16 (88.9)		15 (83.3)		123.4	

$n=77$ after excluding six non-neoplastic lesions

Bold values are statistically significant ($p < 0.05$)

EMR endoscopic mucosal resection

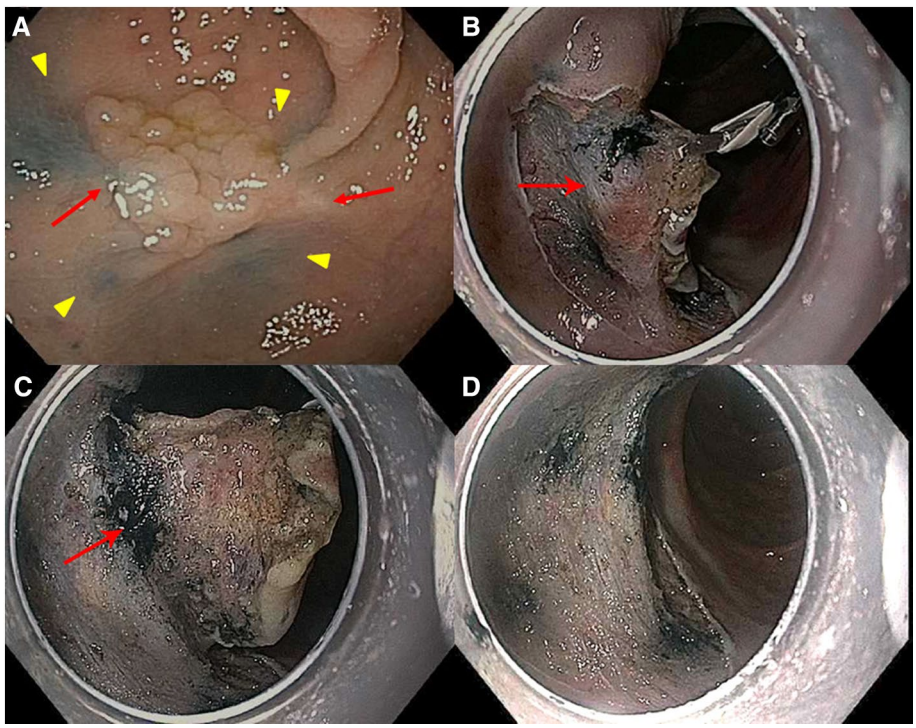

Fig. 1 An example of the various complicating factors that potentially affect clinical outcomes in colorectal ESD. **A** A patient was referred for resection of a non-lifting LST-G lesion in the colon. Tattooed areas (arrowheads) and EMR scars (arrows) are noted. **B** Due to significant submucosal fibrosis (F2) (arrows), the rubber band method was used to provide traction. **C** During submucosal dissection, dense deposits of tattoo ink (arrows) and fibrosis are present in the submucosal layer. **D** Following successful en bloc resection, deposits of tattoo ink are persistently noted on the ESD ulcer bed

(87.0% vs. 96.3%, $p=0.128$). The curative resection rate appeared to be affected by severe fibrosis (83.3%, vs. 94.3% for mild and 100% for no fibrosis, $p=0.092$); however, this did not reach statistical significance.

Procedure time was affected by lesion size > 50 mm (139.4 vs. 90.8 min, $p<0.001$) and by prior EMR attempts (127.8 vs. 94.8 min, $p=0.008$), but not by the presence of tattoo (120.8 vs. 101.4 min, $p=0.209$). Procedure time appeared to be affected by severe fibrosis (123.4 min vs. 106.0 min for mild and 88.7 min for no fibrosis, $p=0.084$); however, this did not reach statistical significance. The adverse event rate was not significantly affected by lesion size ($p=1.000$), the presence of existing tattoo ($p=0.600$), prior EMR attempts ($p=0.100$), or severe fibrosis ($p=0.349$).

On multivariable linear regression analysis (Table 5), the presence of tattoo was an independent predictor for failing to achieve a curative resection (OR 0.13; 95% CI 0.02–0.98; $p=0.048$). Lesion size > 50 mm (OR 3.89; 95% CI 1.13–13.41; $p=0.031$), the presence of tattoo (OR 9.38; 95% CI 1.05–83.83; $p=0.045$), and prior EMR attempts (OR 7.13; 95% CI 1.76–28.90; $p=0.006$) were independent predictors for prolonged procedure time ≥ 90 min.

Scoring system

On a multivariable stepwise regression analysis, lesion size > 50 mm, prior EMR attempts, and presence of tattoo were independent predictors of procedure time being ≥ 90 min. Based on the beta-coefficient of each significant variable, the following scores were assigned: two points for size > 50 mm, three points for presence of tattoo, and three points for prior EMR attempts (Table 5). The probability of colorectal ESD procedure time being ≥ 90 min $= e^{(0.68\times \text{point}-0.73)}/1+e^{(0.68\times \text{point}-0.73)}$.

The scoring system was then externally validated using the Japanese ESD cohort, which included 270 consecutive patients who underwent colorectal ESD for neoplastic lesions. The sensitivity of the scoring system at predicting colorectal ESD procedural time being < 90 min was 100% when the patient had none of the three predicting factors. The specificity of the scoring system at predicting colorectal ESD procedural time being ≥ 90 min was 100% if the patient had at least two of the three predicting factors (total score ≥ 5) (Table 6). The area under the receiver operating characteristics curve (AUC) was 0.78 (95% CI 0.73–0.83) (Fig. 2).

Discussion

ESD is an effective treatment modality for benign, premalignant, and early-stage malignant lesions of the gastrointestinal tract, with favorable outcomes when compared to surgical interventions. However, its use in the US has thus far been limited due to concerns regarding safety, reimbursement, availability and standardization of training, and length of procedure. In a recent systematic review and meta-analysis that demonstrated the safety and efficacy of colorectal ESD, the vast majority of studies were from Asia and only 5/104 studies were from the US [1]. The present study includes our first 83 consecutive colorectal ESD procedures

Table 6 ESD Prediction Model for Colorectal ESD Procedure Time ≥ 90 min

Total score cutoff	Sensitivity (%)	Specificity (%)
≥ 0	100.0	0.0
≥ 2	66.7	91.1
≥ 3	6.1	97.9
≥ 5	0.0	100.0
≥ 6	0.0	100.0
≥ 8	0.0	100.0

Table 5 Multivariable regression analysis of predictors of colorectal ESD outcomes

Predictors	En bloc resection		Complete resection		Curative resection		Procedure time ≥ 90 min		Points for scoring system
	Adjusted OR [95% CI]	*p* value	Adjusted OR [95% CI]	*p* value	Adjusted OR [95% CI]	*p* value	Adjusted OR [95% CI]	*p* value	
Size > 50 mm	0.25 [0.01, 8.56]	0.44	0.25 [0.01, 8.56]	0.44	1.85 [0.17, 19.60]	0.61	**3.89 [1.13, 13.41]**	**0.031**	**2**
Tattoo present	< 0.001 [< 0.001, > 999.999]	0.94	< 0.001 [< 0.001, > 999.999]	0.94	**0.13 [0.02, 0.98]**	**0.048**	**9.38 [1.05, 83.83]**	**0.045**	**3**
Prior EMR	< 0.001 [< 0.001, > 999.999]	0.94	< 0.001 [< 0.001, > 999.999]	0.94	0.40 [0.06, 2.96]	0.37	**7.13 [1.76, 28.90]**	**0.006**	**3**

$n=77$ after excluding six non-neoplastic lesions

Bold values are statistically significant ($p < 0.05$)

CI confidence interval, *EMR* endoscopic mucosal resection, *OR* odds ratio

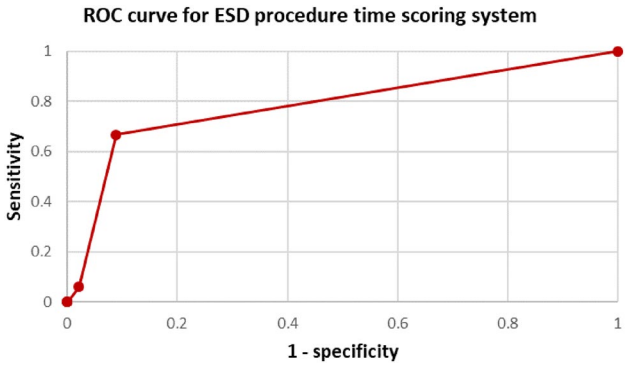

Fig. 2 Receiver operating characteristics curve evaluating the performance of the prediction model for colorectal ESD procedure time. The area under the receiver operating characteristics (AUROC) curve was 0.78 for the external validation cohort (95% confidence internal 0.73–0.83)

at a large tertiary care academic center and represents the largest US series to date. In addition, we successfully developed and validated a scoring system to predict prolonged procedure time in patients undergoing colorectal ESD.

The findings of our study carry relevance among endoscopists in the US for multiple reasons. First of all, the indications for ESD are different in the US than compared to Asian countries. Among Asian countries, ESD is most frequently performed and is considered standard of care for the resection of gastric lesions. Our study reveals that in the US, due to differences in disease prevalence, the vast majority of lesions resected (83.0%) were in the colon and rectum. From a training perspective, this poses additional challenges given that colorectal ESD is associated with greater technical difficulty, increased procedure time, and potentially higher risk of perforation [21].

Another major difference between patients referred for ESD in the US as compared to Asian countries is the lesion characteristics. Among Asian countries, due to ESD being the standard of care for resection of gastric and colorectal lesions, the majority of lesions have minimal or no fibrosis [18]. Our experience is vastly different, with the majority of colorectal lesions having a greater degree of fibrosis (45.5% with mild fibrosis and 23.4% with severe fibrosis). This is a reflection of regional practices in the US, in which lesions are often biopsied and tattooed (16.9% in our cohort) by the initial gastroenterologist. Additionally, EMR is considered the standard endoscopic resection technique in the US, and therefore a substantial number of referred cases have had prior EMR attempts (29.9%). As with previously mentioned differences in lesion location, the greater percentage of fibrotic lesions poses challenges from a training and learning curve perspective.

The findings of our study demonstrate that despite the additional challenges, ESD can be safely, efficiently, and effectively performed in the US for a variety of indications. Among 77 lesions that underwent ESD for colorectal neoplasia, there were only three cases of bleeding and one case of microperforation, with no incidences of major perforation or mortality. There was no recorded incidence of changes in bowel habits, bowel obstruction, or colorectal stricture formation. The vast majority (97.4%) of colorectal ESD patients were managed in an outpatient setting without defect closure, and hospital admission was only required in 2 patients (2.6%). The average ESD procedure time in our cohort was 104.7 min, of which 16.9% of lesions were resected in ≤ 60 min and only 18.2% required > 120 min. An en bloc resection was achieved in 97.4% of cases, complete (R0) resection in 97.4%, and curative resection in 93.5%. In short-term follow-up, there were no cases of recurrence.

One of the major advantages of ESD over EMR is the ability to achieve en bloc resection in situations where patients may have submucosal invasive carcinoma, thus allowing for the potential to achieve a complete resection if margins are negative and curative resection if invasion depth is limited [4]. Of the five patients in our cohort that had submucosal carcinoma, a curative resection was achieved in two patients, and all patients who underwent surgery had no evidence of residual cancer or lymph node metastasis. Although our patients with submucosal invasive carcinoma are presently referred for surgery based on institutional protocol, the ability of ESD to achieve curative resection in a subset of patients with submucosal invasive carcinoma may allow future patients to be spared surgical resection and its associated potential adverse events and costs.

The findings of our study revealed the effect of various factors on procedural outcomes in colorectal ESD performed in the US. We found that the presence of tattoo and prior EMR attempts adversely affected en bloc and complete resection rates on univariable analysis. In addition, the presence of tattoo independently predicted for failure to achieve a curative resection on multivariable analysis. Furthermore, lesion size > 50 mm, presence of tattoo, and prior EMR attempts all independently predicted procedure time ≥ 90 min. These findings may be useful and relevant as endoscopists in the US begin to perform colorectal ESD and are seeking guidance with regards to training, learning curve, and procedure scheduling. Furthermore, the finding that the presence of a tattoo injection negatively affects colorectal resection outcomes further adds to the growing body of literature recommending against this practice when lesions are initially identified [22]. We believe tattoo injections adversely affect colorectal ESD outcomes likely due to the presence of black ink deposits in the submucosal space, which renders identification of the dissection plane challenging. Our findings serve as a strong reminder that prior to referring a patient for colorectal ESD, one should avoid deep biopsies, tattoo injection within or near the lesion, partial

snare resection, or starting an EMR without high confidence of achieving a complete resection.

Even in the hands of a recognized ESD expert, various aspects of our ESD technique are continually evolving. Initial ESD cases were performed using submucosal injection of saline; however, due to technical demands, this was soon replaced by hydroxypropyl methylcellulose, and ultimately hydroxyethyl starch (Hetastarch). When traction was required, the rubber band method [23] and suture loop method were initially used [24]. More recently, given the cumbersome nature of these methods, we adopted the pocket creation method [13]. Although these minor technical modifications did not affect clinical outcomes or adverse events, they illustrate the continual need for ESD practitioners to innovate and adopt new strategies in order to ensure the highest possibility of achieving technical success and ultimately curative resection for the patient.

There are several limitations to our study, which include its limited sample size and retrospective nature. Our study was performed at a major tertiary care academic hospital, and all ESDs were performed by a single recognized ESD expert. Nevertheless, our findings would likely be amplified for less-experienced endoscopists as complicating factors such as presence of tattoo and prior EMR attempts would likely have a greater negative impact on procedural outcomes. As such, we discourage practitioners from attempting such challenging cases early in their learning curve. Additionally, given that patients underwent ESD from 2015 to 2017, long-term follow-up data are still incomplete. However, we would expect our data to be similar to previously published studies on recurrence rates following ESD [25, 26], and expect ESD recurrence rates to be superior to that which has been reported for EMR [27].

In conclusion, colorectal ESD can be safely performed in the US and remains effective despite numerous complicating clinical factors. Prior EMR attempts and placement of a tattoo should be avoided in patients being considered for ESD. A robust scoring system developed using the US cohort and externally validated in the Japanese cohort predicted prolonged ESD procedure time ≥ 90 min with 100% specificity if the patient had at least two of any three predicting factors, and 100% sensitivity if the patient had none of the three predicting factors. The results from this study will provide useful information for predicting resection outcomes and procedure time among endoscopists in the US seeking to incorporate ESD into their practice. Ongoing studies will seek to compare patient and lesion-specific characteristics and clinical outcomes between Asian and US settings.

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Compliance with ethical standards

Disclosures Christopher C. Thompson: Boston Scientific (Consultant) and Olympus (Consultant, Research Support). Hiroyuki Aihara: Boston Scientific (Consultant), Olympus (Consultant), and Fujifilm Medical Systems (Consultant). Drs. Ge, Jirapinyo, Ohya, Tamai, and Sumiyama have no conflicts of interest or financial ties to disclose.

References

1. Akintoye E, Kumar N, Aihara H et al (2016) Colorectal endoscopic submucosal dissection: a systematic review and meta-analysis. Endosc Int Open 4:E1030–E1044
2. ASGE Technology Committee, Maple JT, Abu Dayyeh BK et al. (2015) Endoscopic submucosal dissection. Gastrointest Endosc 81:1311–1325
3. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T et al (2015) Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 47:829–854
4. Tanaka S, Kashida H, Saito Y et al (2015) JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. Dig Endosc 27:417–434
5. Oka S, Tanaka S, Saito Y et al (2015) Local recurrence after endoscopic resection for large colorectal neoplasia: a multicenter prospective study in Japan. Am J Gastroenterol 110:697–707
6. Chung IK, Lee JH, Lee SH et al (2009) Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. Gastrointest Endosc 69:1228–1235
7. Saito Y, Uraoka T, Yamaguchi Y et al (2010) A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). Gastrointest Endosc 72:1217–1225
8. Lee EJ, Lee JB, Lee SH et al (2013) Endoscopic submucosal dissection for colorectal tumors—1,000 colorectal ESD cases: one specialized institute's experiences. Surg Endosc 27:31–39
9. Rex DK, Hassan CC, Dewitt JM (2017) Colorectal endoscopic submucosal dissection in the United States: Why do we hear so much about it and do so little of it? Gastrointest Endosc 85:554–558
10. Horie H, Togashi K, Kawamura YJ et al (2008) Colonoscopic stigmata of 1 mm or deeper submucosal invasion in colorectal cancer. Dis Colon Rectum 51:1529–1534
11. Tanaka S, Oka S, Kaneko I et al (2007) Endoscopic submucosal dissection for colorectal neoplasia: possibility of standardization. Gastrointest Endosc 66:100–107
12. Fujishiro M, Yahagi N, Nakamura M et al (2006) Endoscopic submucosal dissection for rectal epithelial neoplasia. Endoscopy 38:493–497
13. Hayashi Y, Miura Y, Yamamoto H (2015) Pocket-creation method for the safe, reliable, and efficient endoscopic submucosal dissection of colorectal lateral spreading tumors. Dig Endosc 27:534–535

14. Lambert R (2003) The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 58:S3–S43
15. Endoscopic Classification Review Group (2005) Update on the paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 37:570–578
16. Lambert R, Kudo SE, Vieth M et al (2009) Pragmatic classification of superficial neoplastic colorectal lesions. Gastrointest Endosc 70:1182–1199
17. Kudo S, Lambert R, Allen JI et al (2008) Nonpolypoid neoplastic lesions of the colorectal mucosa. Gastrointest Endosc 68:S3–S47
18. Hayashi N, Tanaka S, Nishiyama S et al (2014) Predictors of incomplete resection and perforation associated with endoscopic submucosal dissection for colorectal tumors. Gastrointest Endosc 79:427–435
19. Schlemper RJ, Riddell RH, Kato Y et al (2000) The Vienna classification of gastrointestinal epithelial neoplasia. Gut 47:251–255
20. Kitajima K, Fujimori T, Fujii S et al (2004) Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. J Gastroenterol 39:534–543
21. Uraoka T, Parra-Blanco A, Yahagi N (2013) Colorectal endoscopic submucosal dissection: is it suitable in western countries? J Gastroenterol Hepatol 28:406–414
22. Kim HG, Thosani N, Banerjee S et al (2015) Effect of prior biopsy sampling, tattoo placement, and snare sampling on endoscopic resection of large nonpedunculated colorectal lesions. Gastrointest Endosc 81:204–213
23. Tomiki Y, Ishiyama S, Sugimoto K et al (2011) Colorectal endoscopic submucosal dissection by using latex-band traction. Endoscopy 43(Suppl 2 UCTN):E250–E251
24. Nishizawa T, Uraoka T, Sagara S et al (2016) Endoscopic slipknot clip suturing method: an ex vivo feasibility study (with video). Gastrointest Endosc 83:447–450
25. Isomoto H, Nishiyama H, Yamaguchi N et al (2009) Clinicopathological factors associated with clinical outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms. Endoscopy 41:679–683
26. Park JC, Lee SK, Seo JH et al (2010) Predictive factors for local recurrence after endoscopic resection for early gastric cancer: long-term clinical outcome in a single-center experience. Surg Endosc 24:2842–2849
27. ASGE Technology Committee, Hwang JH, Konda V et al (2015) Endoscopic mucosal resection. Gastrointest Endosc 82:215–226